

Applicants : Philip O. Livingston and Friedhelm Helling
Serial No. : 08/475,784
Filed : June 7, 1995
Page 5

9-14. Support for new claims 54-64 may be found inter alia from pages 11 to 14. Support for new claim 65 may be found inter alia on page 43, lines 4-9. Support for claims 66-72 may be found inter alia on page 15, beginning line 27 to page 18, line 9. Accordingly there is no issue of new matter and applicants respectfully request the entry of this Amendment. Upon entry, claims 53-72 are under examination.

Figure 6

Applicants acknowledge the Examiner's rejection and will provide a new Figure 6, labeling the y-axis as IgG antibodies.

Double Patenting

Applicants acknowledge the Examiner's withdrawal of the provisional rejection.

Obviousness-type Double Patenting

The Examiner provisionally rejected claims 1-4, 6-20 and 44-52 and are under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-20 and 44-52 of co-pending Application No. 08/477,097. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and the co-pending application are both drawn to a vaccine comprising a ganglioside selected from the group consisting GM2, GM3, GD2, GD3, GD3 lactone, O-acetyl GD3, and GT3, or oligosaccharide portion thereof conjugated to an immunogenic protein i.e., KLH thereof, with an adjuvant.

The Examiner provisionally rejected claims 1-4, 6-20 and 44-52 and are under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44, and 46-56 of co-pending Application Nos. 08/477,147 and 08/481,809. The Examiner

Applicants : Philip O. Livingston and Friedhelm Helling
Serial No. : 08/475,784
Filed : June 7, 1995
Page 6

stated that although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the Office Action mailed June 10, 1996.

The Examiner stated that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The Examiner stated that applicants argue the provisional obviousness-type double patenting rejections should be withdrawn in view of applicants arguments under Sections 101, 112 and 103. The Examiner stated that applicants arguments are not persuasive since applicants arguments under 112 and 103 were not found to be persuasive for the reasons set forth below. The Examiner stated that beyond this applicants arguments under 103 or 112 are not persuasive to obviate the rejection since teachings as set forth under 103 or 112 were not used in the provisionally rejected under the judicially created doctrine of obviousness-type double patenting. The Examiner stated that applicants arguments under 101 are not persuasive to obviate the obviousness-type double patenting rejection because although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and the co-pending application are both drawn to a vaccine comprising a ganglioside selected from the group consisting of GM2, GM3, GD α , GD3, GD3 lactone, O-acetyl GD3, and GT3, or oligosaccharide portion thereof conjugated to an immunogenic protein i.e. KLH thereof, with an adjuvant.

The Examiner suggested that applicants provide terminal disclaimers to obviate the obvious type double patenting rejection over the claimed invention of co-pending Application Nos. 08/477,097; 08/477,147; and 08/481,809.

Applicants : Philip O. Livingston and Friedhelm Helling
Serial No. : 08/475,784
Filed : June 7, 1995
Page 7

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of this application, applicants have hereinabove canceled claims 1-4, 6-20 and 44-52 without prejudice. Applicants have added new claims 53-71 in this subject application and have added new claims in U.S. Serial Nos. 08/477,097. Applicants will add new claims in the application's U.S. Serial Nos. 08/477,147 and 08/481,809. Applicants believe that the added new claims in the applications will obviate this ground of rejection.

35 U.S.C. §112, Second Paragraph

Applicants acknowledge the withdrawal of the rejection of claims 4, and 13-17 under 35 U.S.C. 112, second paragraph.

35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1-4, 6-20 and 44-52 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed June 10, 1996.

The Examiner stated that applicants essentially argue the reference by Fung et al. should not be used to question whether antibodies against the ganglioside conjugate vaccines will prevent cancer since the experiments as set forth by Fung et al. were not used to study whether GM2-KLH conjugated vaccine prolonged survivability. The Examiner stated that applicants further argue there is no evidence by Fung et al. that the cancer cells express GM2, nor the antibodies to GM2 were generated after vaccination. The Examiner stated that applicants arguments was to determine the efficacy of the GM2-KLH conjugated vaccine is not sufficient to overcome the rejection. The Examiner stated that as set forth previously since

Applicants : Philip O. Livingston and Friedhelm Helling
Serial No. : 08/475,784
Filed : June 7, 1995
Page 8

the production of high titers of antibodies in melanoma patients with the GM2-KLH does not appear to correlate with the prevention of cancer as exemplified by the teachings of Fung et al., it is unpredictable if the composition as claimed is efficacious as a vaccine. The Examiner stated that beyond this applicants arguments are not sufficient to obviate the rejection since the art as exemplified by Cohen et al. states Cancer vaccines are highly experimental. The Examiner stated that since the specification provide insufficient guidance of how to use the composition as a vaccine and the art at the time of the invention set forth cancer vaccines are highly experimental it is reasonable to conclude a skilled artisan would be forced into undue experimentation to practice the claimed invention.

The Examiner stated that applicants' amendment is sufficient to obviate the objection to the specification for the use of other gangliosides or chemically modified gangliosides. However, the Examiner stated that the specification provides insufficient guidance of how to use derivatives of KLH as recited. The Examiner stated that applicants assert that by routine experimentation one skilled in the art is enabled to make derivatives of KLH. The Examiner stated that applicants arguments are not persuasive.

The Examiner stated that protein chemistry is probably one of the most unpredictable areas of biotechnology. The Examiner stated that for example, replacement of a single lysine residue at position 118 of he acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein. The Examiner stated that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen. The Examiner stated

Applicants : Philip O. Livingston and Friedhelm Helling
Serial No. : 08/475,784
Filed : June 7, 1995
Page 9

that Rudinger et al. teaches particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* must be determined from case to case by painstakingly experimental study. The Examiner stated that Salgaller et al. teach modification i.e. deletions of the amino acid structure of peptide can alter the activity of the protein. The Examiner stated that Fox et al. teach methods for determining fragments which have antigenic activity is unpredictable. The Examiner stated that these references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. The Examiner stated that in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives and fragments encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

In response, applicants respectfully traverse the above ground of rejection. Applicants have hereinabove canceled claims 1-4, 6-20 and 44-52 without prejudice. New claims are directed to a composition comprising a ganglioside conjugated through the ceramide portion of the ganglioside to an immunogenic protein, a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree and a pharmaceutically acceptable carrier and uses of said composition. Accordingly, new claims are not directed to vaccine composition. Accordingly, new claims are not directed to vaccine and thereby render the rejection to the vaccine claims moot.

Regarding the Examiner's comments about other gangliosides, applicants' independent claims now recite clearly the conjugation of the gangliosides occurs through the ceramide portion of the gangliosides. An ordinary skilled artisan can easily use different gangliosides to practice the claimed invention. Accordingly,

Applicants : Philip O. Livingston and Friedhelm Helling
Serial No. : 08/475,784
Filed : June 7, 1995
Page 10

different conjugated gangliosides have been fully enabled by the specification. Applicant believe that the amended claims have obviated this ground of rejection.

Regarding the Examiner's statements about the derivatives of Keyhole Limpet Hemocyanin, applicants maintain that the specification have provided enabling teachings to generate such derivatives. See Specification page 12, lines 4-13. Applicants have also described some routine experiments on page 4, second paragraph of the January 6, 1997 Supplemental Communication in Response to June 10, 1996 Office Action to generate said derivatives. Regarding the Examiner's specific comments about the variation of one or a few amino acids which may change the property of a protein, the disclosed specification has provided specific embodiments of Keyhole Limpet Hemocyanin being used as the immunogenic protein. The derivatives generated may easily be tested using the specific Keyhole Limpet Hemocyanin disclosed in the specification for comparison. Accordingly, there is no undue experimentation and applicants maintain that the derivatives of Keyhole Limpet Hemocyanin are fully enabled by the specification as filed.

In view of the foregoing discussion, applicants respectfully request the reconsideration and withdraw of the above ground of rejection.

§103 Rejection

The Examiner rejected claims 1-3, 6-12, 18-20, 44 and 48-52 under 35 U.S.C. 103 (a) as being unpatentable over Livingston et al. in view of Ritter et al., Livingston et al. (U.S. Patent No. 5, 102,663) and Ritter et al. (1990) for the reasons set forth in the Office Action mailed June 10, 1996.

Applicants : Philip O. Livingston and Friedhelm Hellung
Serial No. : 08/475,784
Filed : June 7, 1995
Page 11

The Examiner stated that in response to applicant's piecemeal analysis of the references one cannot show non-obviousness by attacking referenced individually where, as here, the rejections are based on combinations of references.

The Examiner stated that applicants assert that the cited references do not suggest or motivate one of ordinary skill in the art to make the claimed invention. The Examiner stated that applicants arguments are not persuasive for the reasons as set forth in the last Office Action.

The Examiner stated that applicants appear to argue that the rejection should be withdrawn since from the prior art e.g. Ritter et al. does not suggest or provide an expectation that the oligosaccharide portion of ganglioside conjugate remains intact or needs to be intact. The Examiner stated that applicants arguments are not persuasive to obviate the rejection since applicants arguments are not commensurate in scope with the claimed invention. The Examiner stated that the claimed invention does not set forth that the oligosaccharide portion remains intact. The Examiner stated that beyond this while Ritter et al. (1991) may not characterize that the oligosaccharide portion remains intact with conjugation as asserted by applicants it would have been reasonable to expect the conjugate of the prior art would have been the same properties of the conjugate as claimed such conjugating the KLH to a ganglioside as set forth by Ritter et al. and as recited enhances the antibody response.

The Examiner stated that applicants argue that the rejection should be withdrawn since the prior art does not teach of the requirement e.g. need for an adjuvant. The Examiner stated that applicants argument is not persuasive since Livingston et al. sets forth the vaccine administered to melanoma patient contains an adjuvant.

Applicants : Philip O. Livingston and Friedhelm Helling
Serial No. : 08/475,784
Filed : June 7, 1995
Page 12

The Examiner stated that for the reasons set forth above and in the last Office Action said rejection is maintained. The Examiner rejected claims 4, and 3-17 under 36 U.S.C. 103(a) as being unpatentable over Livingston et al. in view of Ritter et al., Livingston et al. U.S. Patent No. 5, 102,663 and Ritter et al. (1990) as applied to claims 1-3, 6-12, 18-20, 44 and 48-52 above and further in view of Kensil et al. and Marciani et al. for the reasons set forth in the Office Action mailed June 10, 1996.

The Examiner stated that applicants appear to argue the rejection should be withdrawn since the prior art does not suggest or provide an expectation of making the claimed invention as applied to claims 1-3, 6-12, 18-20, 44 and 48-52 above. The Examiner stated that for the reasons set forth above applicants arguments are not persuasive.

The Examiner stated that applicants assert that Kensil et al. and Marciani et al. do not suggest or motivate one of ordinary skill in the art to make the claimed invention. The Examiner stated that applicants arguments are not persuasive for the reasons as set forth in the last Office Action.

In response, applicants respectfully traverse the above ground of rejection. Applicants would like to point out the applicants have canceled claims 1-4, 6-20 and 44-52 without prejudice. New claims are directed to a composition comprising a ganglioside CONJUGATED THROUGH THE CERAMIDE PORTION of the ganglioside to an immunogenic protein, a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree and a pharmaceutically acceptable carrier and uses of said composition.

Applicants maintain the cited references, alone or in combination thereof do not disclose, teaches or suggest the conjugation of a

Applicants : Philip O. Livingston and Friedhelm Helling
Serial No. : 08/475,784
Filed : June 7, 1995
Page 13

ganglioside through the ceramide portion of the ganglioside to an immunogenic protein. The cited references, alone or in combination thereof, do not provide any SPECIFIC teaching that the conjugation should be carried at the ceramide portion. In addition, applicants further maintain that the cited references do not disclose, teaches or suggest the composition comprising the above ganglioside conjugates and a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree.

Accordingly, in view of the foregoing, applicants respectfully request the reconsideration and withdraw of the above ground of rejection.

The Examiner rejected claims 45-47 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. in view of Ritter et al., Livingston et al. U.S. Patent No. 5, 102,663 and Ritter et al. (1990) as applied to claims 1-3, 6-12, 18-20, 44 and 48-52 above and further in view of Irie et al. for the reasons set forth in the Office Action mailed June 10, 1996.

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of this subject application, applicants have hereinabove cancel claims 45-47 without prejudice. New claim 68 corresponds to the canceled claims 47 except that it ultimately depends on claim 53 which recites a composition comprising a ganglioside conjugated through the ceramide portion of the ganglioside to an immunogenic protein, a carbohydrate derivable from the bark of a Quillaja saponaria Molina tree and a pharmaceutically acceptable carrier. The additional citation of Irie et al. in combination with the previous cited reference does not render the composition claim, claim 53 obvious and therefore cannot render the dependent claim 68 obvious.

Applicants : Philip O. Livingston and Friedhelm Helling
Serial No. : 08/475,784
Filed : June 7, 1995
Page 14

Accordingly, applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

In summary, for the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection set forth in the September 3, 1997 Office Action and earnestly solicit allowance of the claims now pending in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the FOUR HUNDRED AND SEVENTY-FIVE DOLLAR (\$475.00) fee for a three-month extension of time is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Albert Wai-Kit Chan

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Assistant Commissioner for Patents,
Washington, D.C. 20231.

Albert Wai-Kit Chan 3/3/98
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